UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,353	11/14/2003	Janine Schuurman	GMI-059	6363

959 7590 09/07/2006

LAHIVE & COCKFIELD
28 STATE STREET
BOSTON, MA 02109

EXAMINER	
BRISTOL, LYNN ANNE	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 09/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/714,353	SCHUURMAN ET AL.	
	Examiner	Art Unit	
	Lynn Bristol	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24,28-30,32-34,36-38 and 40-104* is/are pending in the application.

4a) Of the above claim(s) *57-66,68-98,103 and 104* is/are withdrawn from consideration.

5)☒ Claim(s) *51,52 and 99-102* is/are allowed.

6)☒ Claim(s) *1-24,28-30,32-34,36-38,40-50,53-56,67,103 and 104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/28/04; 11/14/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 25-27, 31, 35 and 39 are cancelled by amendment. The amendment of Claims 12, 14, 16, 18, 22-24, 28-30, 32-34, 36-38, 40-46, and 48-50 in the Reply of June 29, 2006 is acknowledged as finding support in the original claims or specification as filed, and has been entered. New claims 99-104 are drawn to embodiments for each of AB12, AB1, AB7 and AB11 and are supported in the original claims and specification as filed, and have been entered.

2. The amendment to the specification to include sequence identifiers for Figures 1 and 2 in view of the revised Sequence Listing has been considered and entered.

3. Claims 1-24, 28-30, 32-34, 36-38 and 40-104 are all the pending claims.

4. Claims 57-66, 68-98 are withdrawn.

5. Claims 1-24, 28-30, 32-34, 36-38, 40-56, 67, and 99-104 are all the claims under examination.

Election/Restrictions

6. In the telephonic interview with Applicants on June 14, 2006, the Examiner agreed to examine a first elected CDR3 and corresponding variable regions from one of the claimed antibody embodiments for AB 12, Ab1, Ab7 and AB11, and agreed that should the CRD3 and corresponding variable regions for one antibody be found free of prior art, the remaining three antibodies would be searched.

Applicant's timely filed an election with traverse of Group 12 (Claims 32-35- drawn to AB12) in the reply filed on June 29, 2006, wherein Applicant's have provided

the breakdown of the claimed antibody embodiments for AB 12, Ab1, Ab7 and AB11 set forth in the chart on pp. 23-24. The traversal is on the ground(s) as discussed during the telephone interview and reiterated in the Reply that all of the antibodies bind to CD25 and that searching each and every embodiment would not be unduly burdensome. In view of Applicants having amended the claims to more clearly set forth the antibody embodiments, the interview discussion, and the amendment of claims to include sequence identifiers to facilitate searching, the Examiner has withdrawn the restriction for the isolated human antibody claims. Accordingly, Claims 1-24, 28-30, 32-34, 36-38, 40-56, 67, and 99-104 are all the claims under examination.

Information Disclosure Statement

7. The US patent, international and foreign patent references as well as the nonpatent literature references cited in the IDS' of May 28, 2004 and November 14, 2005.

Specification

8. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (p.9, line 7; p. 57, lines 11-12). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The use of the trademark Zenapax® has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 12, 14, 16, 18, 19 and 56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 12, 14, 16, 18, 19 and 56 are each drawn to a human monoclonal antibody comprising HC and LC variable domains with binding specificity for CD25 where the variable domains are at least 90% homologous to the variable domains for the HC and LC of AB7 (Claim 12 and 19), AB12 (Claim 14 and 19), AB1 (Claim 16 and 19) and AB11 (Claim 18 and 19).

The specification teaches antibodies and antibody fragments in general [0074-0075]; and more specifically human antibodies specifically excluding antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, grafted onto human framework sequences [0081]; producing the human

monoclonal antibodies by a hybridoma which includes a B cell obtained from a transgenic or transchromosomal nonhuman animal, e.g., a transgenic mouse, having a genome comprising a human heavy chain transgene and a light chain transgene, fused to an immortalized cell [0082-0083; 0123-0126] or transfectoma [0084, 0132-0133]; conservative sequence modifications [0102-0103]; and the CDR1, 2, and/or 3 of the engineered antibodies comprising the exact amino acid sequence(s) as those of AB1, AB7, AB11, or AB12 or the engineered antibody may be composed of one or more CDRs that are, for example, 90% to one or more CDRs of AB1, AB7, AB111, or AB12 [0152].

The specification does not provide sufficient written description as to the structural features of the claimed genus of human monoclonal antibodies for CD25 and the correlation between the chemical structure and function of the genus of the antibodies, such as structural domains or motifs that are essential and distinguish members of the genus from those excluded. Additionally, the specification does not disclose a single species of a human monoclonal antibody with VH, VL or CDR1-3 having less than 100% sequence identity for the corresponding domains of the parent antibody for any one of AB7, AB12, AB1 or AB11.

A "representative number of species" means that the species, which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if

the disclosure "indicates that the patentee has invented species sufficient to constitute the genus. " See Enzo Biochem, 323 F.3d at 966, 63 USPQ2d at 1615; Noelle v. Lederman, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). "A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." In re Curtis, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004)(Claims directed to PTFE dental floss with a friction-enhancing coating were not supported by a disclosure of a microcrystalline wax coating where there was no evidence in the disclosure or anywhere else in the record showing applicant conveyed that any other coating was suitable for a PTFE dental floss.).

In the absence of sufficient guidance and direction to the structural and functional analysis, applicant's reliance on the CD25 binding activity of the human monoclonal antibodies AB7, AB12, AB1 or AB11, disclosed in the specification as-filed does not appear to provide sufficient written description for the genus of human anti-CD25 monoclonal antibodies encompassed by the claimed specificities in view of the above evidence, which indicates ordinary artisans could not predict the operability in the invention of just any species other than disclosed for AB7, AB12, AB1 or AB11.

For inventions in an unpredictable art, adequate written description of a genus, which embraces widely variant species cannot be achieved by disclosing only one species within the genus. In the instant case, applicant has not even disclosed a single species encompassed by the human monoclonal antibodies AB7, AB12, AB1 or AB11comprising a VH, VL or CDR sequence having at least 90% identity or homology with the corresponding VH, VL or CDR of the parent antibody. See, e.g., Eli Lilly. Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. If a representative number of adequately described species are not disclosed for a genus, the claim to that genus must be rejected as lacking adequate written description under 35 U.S.C. 112, first paragraph.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of human anti-CD25 monoclonal antibodies, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a

potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddles v.Baird, 30 USPQ2d 1481, 1483. In Fiddles v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Therefore, only those human monoclonal antibodies AB7, AB12, AB1 or AB11, but not the full breadth of claims 12, 14, 16, 18, 19 and 56 meets the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

10. Claims 7-24, 28-30, 32-34, 36-38, 40-50, 53, 54, 56, 67, 103 and 104 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making fully human anti-CD25 (IL-2 receptor) monoclonal antibodies with the XenoMouse technology having a K_D of about 10^{-8} M or less, the anti-CD25 antibodies AB7, AB12, AB1 or AB11 and using the antibodies to: inhibit binding of IL-2 to CD25; inhibit anti-CD3 induced T cell proliferation of PBMCs; inhibit MLR; and internalize CD25 expressed on T cells, does not reasonably provide enablement for making or using just any human monoclonal antibodies which inhibit IL-2 binding to CD25, or just any human anti-CD25 monoclonal antibodies with VH, VL and CDRs

having at least 90% homology to the parent antibodies, AB7, AB12, AB1 or AB11, much less that any or all of the human antibodies having at least 90% homology would inhibit IL-2 binding to CD25. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to practice the invention as claimed.

The interpretation of Claims 12, 14, 16, 18, 19 and 56 is discussed under section 9, supra. Claims 1-6, 53-55 and 67 are drawn to just any isolated human monoclonal antibody having the property of inhibiting IL-2 binding to CD25. Claims 7-11, 13, 15, 17, 20-24, 28-30, 32-34, 36-38, 40-50, 103 and 104 are drawn to the nucleotide sequences encoding or the amino acid sequences for human monoclonal antibodies AB1, AB7, AB11, and AB12 comprising sequence modifications in the HC and LC variable regions and CDRs for the respective antibodies.

The interpretation of the specification with respect to providing support for human anti-CD25 monoclonal antibodies having 90% homology to the VH, VL and CDR1-3 for any one of AB1, AB7, AB11, and AB12 is discussed supra under section 12. It is

emphasized that no examples are provided for any human monoclonal antibody having less than 100% homology to AB1, AB7, AB11, and AB12. Further, the specification does not disclose any functional antibodies where substitutions have been introduced into the nucleotide sequence encoding or the amino acid sequence for any one of CDR1-3 of the HC or LC of AB1, AB7, AB11, and AB12. The specification teaches and demonstrates the following properties for only the full human monoclonal antibodies AB1, AB7, AB11, and AB12: inhibition of IL-2 binding to its receptor, CD25, by supernatants of human monoclonal antibodies AB1, AB7, AB11, and AB12 (FIG. 11); inhibition of anti-CD3 antibody-induced T cell proliferation (using PBMCs) (Fig 13); inhibition of MLR (FIG. 14); and internalization of CD25 by FITC-labeled AB12 (FIG. 15). The specification does not demonstrate a human monoclonal antibody having at least 90% homology to its respective parent antibody having the property of inhibiting IL-2 binding to CD25.

-) The specification is not enabled for making or using a human anti-CD25 monoclonal antibody having VH, VL or from 1 to 3 CDRs having at least 90% homology with the VH, VL or CDRs of AB1, AB7, AB11, and AB12.

The claims are not commensurate in scope with the enablement provided in the specification because the specification does not disclose any species for human anti-CD25 monoclonal antibodies having at least 90% sequence identity with the VH, VL or CDRs for the corresponding regions of AB1, AB7, AB11, and AB12. The specification does not support the broad scope of the claims which encompass all modifications to

the VH, VL and CDR1-3 of AB1, AB7, AB11, and AB12 because the specification does not disclose the following:

The general tolerance to modification and extent of such tolerance;

The specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical; and

The specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed human anti-CD25 monoclonal antibody in a manner reasonably correlated with the scope of the claims broadly including any number of additions, deletions, or substitutions. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970).

Without such guidance, the changes which can be made in the protein's structure and still maintain biological activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F,2d 1200, 18 USPQ 1016 (Fed. Cir. 1991) at 18 USPQ 1026 1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986).

Further protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al,

Journal of Cell Biology Vol 111 November 1990 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252). Additionally, other references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein. For example, replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin. Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411 (1987). Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase. Lin et al Biochemistry USA Vol 14:1559-1563 (1975).

With regard to predictability of making a human anti-CD25 monoclonal antibody with modifications to for example, the CDRs and framework regions, it is well known that amino acid changes in the variable regions of antibodies can have a drastic effect on conformation and function.

1) The specification teaches and the claims encompass introducing modifications into the framework for the AB1, AB7, AB11, and AB12 antibodies, but the only VH and VL domain frameworks used are the native frameworks for these clones. It is not expected that just any modified framework comprising the VH or VL domain of the human anti-CD25 monoclonal antibody can be generated without effecting the binding

activity. Queen et al. (USPN 5530101; published June 25, 1996; filed December 19,1990) disclose methods for humanizing antibodies and selecting only human immunoglobulin framework sequences having the most homology to the framework of the donor antibody (Col. 2, line 35-58) where the homology is substantially identical (about 85% or more, usually 90-95% or more) to the framework region of a naturally occurring human immunoglobulin (Col. 11, lines 44-52). Queen discloses the criticality of the framework in preserving the affinity of CDRs for the original antigen when donor CDRs are engineered into an acceptor framework (Col. 12, line 46- Col. 14, line 51).

2) The specification teaches and the claims encompass introducing modifications into the CDRs for the AB1, AB7, AB11, and AB12 antibodies, but the only CDRs shown to have been isolated by Applicants and demonstrated to have IL-2 binding inhibitory activity, are the native CDRs for the VH and VL of the AB1, AB7, AB11, and AB12 antibodies. It is well accepted that even minor changes in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al. (Proc. Natl. Acad. Sci USA 1982 79:1979). Rudikoff teaches that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

Thus, it is unlikely that human anti-CD25 monoclonal antibodies as defined by the claims, i.e., modifications to the variable regions, and which may contain both framework and CDR substitutions for the heavy and light chain variable regions in unspecified order, have the required binding function. Therefore, producing just any human anti-CD25 monoclonal antibodies having binding specificity and affinity for CD25

much less the ability to inhibit IL-2 binding would be unpredictable based on the methods described in the specification and the prior art disclosures.

Therefore, in view of the broadly claimed invention, the lack of predictability in the art as evidenced by Burgess, Lazar, Schwartz, Lin, Queen and Rudikoff, and lack of guidance in the specification with regard to producing and/or using the human anti-CD25 monoclonal antibodies, one of skill in the art would be required to perform undue experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. Claims 1-6 and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Green (J. Immunol. Methods 231:11-23 (1999); hereinafter referred to as "Green") in view of Osterberg et al. (Biochemical Society Transactions 23:1038-1043 (1995);

hereinafter referred to as "Osterberg") and/or Henry et al. (Expert Opin. Pharmacother. 3(11):1657-1663 (2002); hereinafter referred to "Henry").

Claims 1-6 and 55 are drawn to an isolated human monoclonal antibody, which binds human CD25 and inhibits IL-2 binding to CD 25, is IgG1, IgG2, IgG4 or IgM, and has a K_D of 10^{-9} M or less using surface plasmon resonance technology in a BIAcore instrument, and antibody fragments.

Green discloses the XenoMouse technology for generating large panels of high-affinity, fully human antibodies with the pharmacokinetics of normal human antibodies (Fig. 1; p. 19, Col. 1, ¶3; p. 21, Col. 1, ¶1); that the immune system of the XenoMouse strains recognize administered human antigens as foreign, and with a strong human humoral immune response with the use of XenoMouse mice in conjunction with well-established hybridoma procedures reproducibly results in IgG mAbs with sub-nanomolar affinities for human antigens with suitability for repeated administration to human (p. 13, Col. 2, ¶1); generating IgG monoclonal antibodies to human proteins that are totally novel to a mouse or that are 100% identical to a mouse homolog (p. 18, Col. 1, ¶1); producing IgM_k, $IgG1_k$, $IgG2_k$ or $IgG4_k$ mAbs depending on the XenoMouse strain (p. 18, Col. 1, ¶2); and mAbs with K_D of between 10^{-11} and 10^{-9} M determined by solid phase measurements using surface plasmon resonance in the BIAcore system (p. 18, Col. 2, ¶2). Green does not disclose making fully human anti-CD25 monoclonal antibodies having the ability to inhibit IL-2 binding. Osterberg and Henry rectify this deficiency in there disclosures.

Osterberg discloses humanized anti-Tac (IL-2 receptor complex) antibodies having computer modeled human V region framework sequences (p. 1039, Col. 2, ¶3), and contemplates producing fully human antibodies to reduce the immunogenecity problem with chimeric or humanized antibodies (p. 1039, Col. 1, ¶2)

Henry discusses and compares the IL-2 receptor antibodies, basiliximab (mouse/human chimera) and daclizumab (humanized) (Table 1), and teaches antibody fragments (Fab) (p. 1658, Col. 1, ¶2) and that basiliximab inhibits IL-2 binding (Abstract; p. 1658, Col. 1, ¶2), but that in some transplantation studies in human trials, the antibody is not 100% effective with there being some incidence of acute rejection and limited side effects (p. 1660, Col. 1, ¶2- p. 1661, Col. 1661, Col. 2, ¶4).

It would have been *prima facie* obvious at the time the invention was made to have produced the human anti-CD25 monoclonal antibody having all of the claimed properties in view of the combined disclosures of Green, Osterberg and Henry.

One of ordinary skill in the art would have been motivated and had a reasonable expectation of success in combining the reference disclosures of Green, Osterberg and Henry because Green teaches away from humanization of antibodies stating that:

> "the technology requires individual tailoring for each antibody, including extensive molecule modeling and manipulation of the DNA encoding the mAb. Even then, amino acid changes that would be predicted to have little effect on the antibody could unexpectedly abrogate antibody function. Finally, humanization leaves murine amino acids in the antibody, allowing the possibility of a HAMA [human anti-mouse antibody] response." (p. 12, Col. 1, ¶4- p. 13, ¶1),

and specifically teaches the advantages of XenoMouse technology to produce a vast array of fully human antibodies with reduced immunogenicity. Further in view of Osterberg's disclosure of the advantages human monoclonal antibodies in the context of the humanized anti-Tac antibody, and Henry's disclosure that anti-CD25 antibodies with IL-2 binding inhibitory activity are essential for specific T-cell targeting in disease treatment (despite the limited side effects of basiliximab), in addition to the availability of the XenoMouse technology to generate a fully human antibody repertoire against a single human antigen, one skilled in the art would have been motivated to have produced and would have been assured of success in producing and selecting a human monoclonal anti-CD25 antibody with IL-2 binding inhibitory activity as well as the instant claimed isotype repertoire, a K_D of 10^{-9} M or less and antibody fragments. Thus the claims were prima facie obvious at the time of the invention in view of Green, Osterberg and Henry.

Conclusion

12. Claims 51, 52 and 99-102 appear to be allowable over the prior art. The closest prior art embodiments are the chimeric and humanized anti-CD25 antibodies, basiliximab and daclizumab, respectively, and are well known in this field of art (Pascual et al. Nephrol Dial Transplant 16:1756-1760 (2001); Henry et al. (Expert Opin. Pharmacother. 3(11):1657-1663 (2002)). None of the prior art anti-CD25 antibodies anticipate or render obvious an isolated human anti-CD25 antibody having a heavy chain variable region derived from a human V_H1-69/JH4b or V_H1-69/JH5b germline

sequence and light chain variable region derived from a human A27/J_k4 or A27/J_K5 germline sequence; an isolated human anti-CD25 antibody having a heavy chain variable region derived from a human V_H1-69/D7-27/JH4b or V_H1-69/ D7-27/JH5b germline sequence and light chain variable region derived from a human A27/J_k4 or A27/J_K5 germline sequence; a human anti-CD25 antibody that inhibits IL-2 binding to CD25 and has VH CDR1-3 comprising SEQ ID NOS:35-37 and VL CDR1-3 comprising SEQ ID NOS:38-40; or a human anti-CD25 antibody that inhibits IL-2 binding to CD25 and has VH CDR1-3 comprising SEQ ID NOS:17-19 and VL CDR1-3 comprising SEQ ID NOS:20-22.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LAB

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER